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CURRENT DRUG TREATMENT OF HYPERTENSION*

The management of patients with hypertension continues to be a subject of much controversy. This paper by Dr. Robert W. Wilkins is the second of two articles dealing with this problem. The first article, by Dr. Samuel Proger, appeared in the October issue of MODERN CONCEPTS OF CARDIOVASCULAR DISEASE. The editors believe that the two different points of view expressed by Dr. Wilkins and Dr. Proger will be of interest to the reader.

The treatment of essential hypertension as of any chronic disease with a large functional component is a matter for the art as well as the science of medicine. It requires judgment, a thorough knowledge of the disease in the individual patient, and broad experience with the various therapeutic measures available for use. In these respects the therapy of hypertension resembles that of peptic ulcer in which psychotherapy, dietotherapy, the regulation of habits, and the use of drugs and even surgery may play varied roles in different patients. Since etiology is unknown, one must proceed on the basis of hypothesis as to the nature of the disease. The hypothesis upon which the drug therapy of essential hypertension discussed in this paper is based is as follows:

1. Essential hypertension is a disease which begins as a functional (intermittent) elevation of arterial blood pressure, probably due to a familial (? hereditary) tendency to this pattern of response.

2. Emotional (psychogenic), renal, and endocrine factors may, and frequently do, contribute to the functional elevation of pressure.

3. Early, and sometimes even late after the appearance of this type of elevation of pressure, it is completely reversible.

4. The elevation of pressure is not the most important disturbance that may be produced. It places a strain on the cardiovascular system and leads to, or at least aggravates structural (organic) hypertensive cardiovascular-renal disease. Three areas in particular are vulnerable, the cardiac, the cerebral, and the renal. Evidences of hypertensive vascular disease in these areas should be sought for and should be used as diagnostic and prognostic signs. Lowering the blood pressure is one means of lessening hypertensive cardiovascular strain and disease.

5. The progression of organic hypertensive cardiovascular disease may be slow, rapid, or intermittent, and occasionally may even spontaneously reverse itself. In part this may be determined by familial factors, but emotional, renal, endocrine, and probably dietary factors also are important. When the renal disease associated with essential hypertension becomes critical, a vicious circle may be established, in which a true "renal" hypertension of serious import is superimposed.

6. No clear-cut or exclusive separation can be made between various stages, types, or degrees of the disease. Thus, any benign hypertension may become severe, any severe hypertension may become malignant, and occasionally a malignant hypertension may spontaneously become less severe or even benign, although the latter events occur rarely because the cardiovascular-renal disease associated with the malignant stage is very difficult to reverse.

On the basis of this hypothesis, therefore, the goals of therapy are not only to treat the existing disease but also to prevent, if possible, its progression into a more severe form. By this very token, however, one certainly is not justified in treating all hypertensive patients, even those with equally elevated pressures, in the same way. The "punishment" should be made to fit the "crime"; the treatment should be selected to fit the disease. A milder disease merits at least a trial of milder therapy, but it should nevertheless be treated (if only by psychotherapy) in the hope of not only relieving symptoms but preventing more serious elevations of pressure and greater cardiovascular disease. To delay the treatment of hypertension until every evidence of the severest forms of or-

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ganic disease are present may be to delay too long. It may be "locking the door after the horse is stolen".

Admittedly, only time will tell whether this approach to therapy prolongs the lives and improves the mortality statistics of hypertensive patients. Fortunately, however, mortality statistics are not the *only* criterion of the success of therapy. Relief of symptoms, improvement in signs, and increases in cardiovascular reserve are valid criteria if adequate control observations have been made. Much clinical evidence is now accumulating to support the belief that treatment of even mild essential hypertension is most worthwhile. Obviously, in such an appraisal the benefits, both real and potential, must be weighed against the ill effects, real and potential, of drugs, surgery, diets, psychotherapy and of no treatment at all. It should also be clear that under this approach "treatment" does not mean exclusively drug treatment, surgical treatment or any other single procedure. It does mean that the treatment is "hypotensive", that is, has as one of its aims lowering the blood pressure of the hypertensive patient, because to do this lessens his cardiovascular-renal disease.

Selection of Patients

There is no sure method of deciding in advance which hypertensive patient will respond to which hypotensive drug. This must be discovered by trial and error. The patient is first evaluated on the basis of a careful history, physical examination (including fundoscopy), and laboratory studies such as electrocardiographic, roentgenographic and chemical evidences of cerebral, cardiac, and renal function. Signs and symptoms of severe, organic, hypertensive vascular disease and dysfunction, especially in the kidneys, may increase the desirability, but will decrease the probability of favorable results from any type of hypotensive therapy, medical or surgical. Actual uremia is a bad omen. Cardiac impairment, particularly coronary ischemia and congestive failure, are serious signs. However, coronary, or even cerebrovascular, ischemia or occlusion, are not absolute contraindications to trials of hypotensive drugs. They are definite warnings to institute such agents gradually, starting with the milder drugs, adding the stronger ones with greatest caution (particularly hydralazine). Marked retinopathy, on the other hand, while a serious prognostic sign in hypertensive patients without hypotensive therapy, is no contraindication to such therapy, and indeed may be one of the most striking and early of the objective signs to improve if blood pressure can be lowered. Age (over 50), sex (male), and weight (obesity) are important (unfavorable) factors. The actual level of the blood pressure is of less importance unless the diastolic pressure is over 140 and will not fall on bed rest or sedation. A rapid pulse rate before treatment generally indicates that a favorable effect may follow the use of pulse-rate-slowing drugs such as Rauwolfia or veratrum. However, if tachycardia persists on treatment it usually is an unfavorable sign, and may indicate incipient or actual myocardial failure which should be treated by the usual methods.

Selection of Drugs

Since such a variety of drugs has been used with reported success in hypertension, it is difficult to believe that any one of them (or for that matter, any other form of treatment) can be specific. For this reason there is no necessity of being committed exclusively to any one drug. A selection can be made of that regimen which proves to be the most beneficial in proportion to the degree of disturbance it causes in the given patient. It is now also generally agreed that combinations of drugs are usually more satisfactory than any one drug alone. Undoubtedly this arises in part from the well known pharmacological principle of adding the desirable effects common to different agents, while scattering or actually counterposing their indifferent or undesirable effects.

In general, the various hypotensive drugs may be said to produce unfavorable side effects in rough proportion to their acute hypotensive power. That is to say, the more powerful a drug is as an acute blood-pressure-lowering agent, the more likely it is to cause trouble. Since the hypotensive effects of any drug in any given patient are unpredictable, it seems wiser to begin treatment of a new patient with the milder, less disturbing agents and to turn to severer symptom-producing drugs only after adequate trial (6 weeks) of a milder regimen proves to be ineffectual.

Only those drugs which can be taken chronically by mouth will be considered here. They will be discussed in order of their increasing potency and side effects. Rauwolfia, as the crude powdered root (Raudixin*) or as the extract (Rauwiloid**), is a sedative and mildly hypotensive drug which slows the pulse rate and causes nasal stuffiness. Its effects are slow to appear and to disappear and it is usually well tolerated, although in time on full dosage it may cause ex-

* E. R. Squibb & Sons, New York City.
** Riker Laboratories, Incorporated, Los Angeles, California.

cessive drowsiness or nightmares. It is particularly useful alone for relieving young, labile, psychoneurotic hypertensive patients with tachycardia. It also is an excellent adjunct or "background drug" for smoothing the action and moderating the side effects of the other more potent hypotensive agents. It allows such agents to be used successfully in smaller doses than is possible alone.

Veratrum, either as an extract (Veriloid,* Vergitryl**) or as a pure alkaloid (Protoveratrine), is a powerful, centrally-acting neurogenic vasodilator which slows the pulse rate. Unfortunately, it has a narrow dosage range limited by the appearance of nausea and vomiting. Hydralazine (Apresoline***) is a central adrenergic-blocking drug that causes renal vasodilatation and tachycardia. Its many possible side effects, including headache and palpitation, will be discussed later. It is particularly useful in conjunction with Rauwolfia, or in very severe cases, with hexamethonium. Hexamethonium is a total ganglionic blocking agent capable of producing profound (and especially postural) hypotension. Its dosage and absorption characteristics are highly unpredictable and its side effects are so marked and widespread that it should never be instituted outside of a hospital. Many workers believe that it should be given only by parenteral administration.

Plan of Treatment

A common plan of treatment of an uncomplicated case of essential hypertension is to begin with the mildest agent, Rauwolfia, 100 milligrams (or equivalent) two to four times a day. This will usually relieve symptoms such as anxiety, headache, and palpitation and often will lower the blood pressure, especially in the only moderately severe, labile hypertensive patient who has tachycardia before treatment. If this does not suffice after several weeks' trial, either hydralazine (if the pulse rate is slow) or veratrum (if the pulse rate is above 80) may be added to the Rauwolfia in gradually increasing doses as necessary. It is usually better to begin hydralazine at a low dose, 10 milligrams four times a day, gradually increasing to at least 50 milligrams four times a day. This arrangement usually moderates the initial side effects such as intolerable headache and palpitation (tachycardia). A few patients will not be able to take hydralazine even in combination with Rauwolfia, usually because of the headache. Patients with possible or probable coronary disease should be placed on hydralazine only if they do not have tachycardia since they are liable to suffer anginal attacks (with adverse electrocardiographic changes) on this drug (see below). Veratrum may be given either as an extract (e.g. Veriloid, 2 milligrams four times a day), or as a pure alkaloid (e.g. protoveratrine, 0.25 milligram four times a day) increasing the dose gradually as necessary and as tolerated by the patient without nausea and vomiting. When given together with Rauwolfia, veratrum seems to cause less nausea and vomiting in relation to its hypotensive effect than when given alone.

In some patients all three drugs (Rauwolfia, hydralazine, and veratrum) must be given together to get the desired hypotensive effect. This is quite feasible since they can be given in the same oral dosage schedule and are usually well tolerated in combination. When several weeks of trial of all three of these drugs in maximum tolerable dosage still does not suffice to control the blood pressure in progressively severe hypertensive patients, it may be justifiable to try hexamethonium. However, in stable, non-progressive hypertensive patients it is usually preferable merely to persist for a longer period with the trial of the other three agents in various doses. Probably no single factor is more important for successful drug treatment of hypertension than patient persistence.

Hexamethonium should always be instituted in a hospital and with greatest caution. (Rauwolfia and/or Apresoline are usually continued.) It may be given either orally (starting dose 25 mg.) or parenterally (starting dose 2.5 mg.) but the oral route is considerably more difficult to manage. For this reason some authorities recommend that it always be given parenterally, because it is so poorly and erratically absorbed by mouth. Furthermore, tolerance develops rapidly so that increasing doses usually have to be given to get an effect. The dosage, therefore, is quickly raised stepwise on each succeeding dose until either some hypotension (at least in the upright position) or some side effects are produced, whereupon this dosage is maintained (or slowly increased) and given 2 to 4 times a day as necessary to achieve the desired hypotensive reaction.

Since hexamethonium is a total ganglionic blocking agent, it causes not only postural hypotension but also blockade of other autonomic functions including those of the accommodation of the eye and the motility of the bowel and bladder. These side effects, particularly the con-

* Riker Laboratories, Incorporated, Los Angeles, California.
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*** Ciba Pharmaceutical Products, Incorporated, Summit, New Jersey.

stipation, must be counteracted by the proper symptomatic therapy although, as tolerance develops, they may become less troublesome. When the correct dosage of hexamethonium to maintain the desirable results has been determined, the patient is discharged, preferably in the care of a member of the family who is taught how to measure the blood pressure before each dose of the drug and to adjust the dosage accordingly. Obviously this complicated procedure is far from ideal. It is considered to be justifiable only in desperate cases in whom the prognosis certainly is very poor without such management. There is no question that hexamethonium therapy is immeasurably more difficult to manage successfully than any other medical regimen for hypertension, even when used in conjunction with Rauwolfia which seems to make it considerably less troublesome than it is alone.

Complications and Precautions

The side effects of the several drugs which are now in general use for the medical treatment of hypertension have been mentioned. Worthy of additional emphasis are the signs and symptoms of myocardial ischemia particularly in association with the use of hydralazine and hexamethonium. Hydralazine seems to produce this effect only in those patients who may have coronary disease. It does not necessarily require a hypotensive reaction for myocardial ischemia to occur under this therapy. The symptoms of angina on hydralazine are not usually related to effort but may resemble a status anginosus. They are accompanied by the electrocardiographic evidences of myocardial ischemia. On the other hand, the angina following hexamethonium seems to be definitely related to its hypotensive effect, particularly in the upright position, and patients must be cautioned to lie down if they have this symptom after taking hexamethonium. Besides the danger of myocardial ischemia and thrombosis from powerful hypotensive drugs there is always the danger of cerebral thromboses during severe hypotensive episodes. It also seems not unlikely that renal shutdown which has followed the use of the stronger agents on occasion is due to too sudden and precipitous a collapse of the pressure. All of these dangers emphasize the wisdom of instituting hypotensive therapy with the milder agents and of proceeding very gradually with the aim of lowering the pressure smoothly and slowly rather than suddenly and dramatically.

Hydralazine from its structural formula might be expected to depress the bone marrow. However, there is only one reported case of pancytopenia following the use of this drug. There have been several cases of large gastrointestinal hemorrhage in patients taking hydralazine but in at least two of these there was no previous abnormality of the blood. It is interesting to speculate that autonomic blockade of adrenergic impulse might allow unopposed cholinergic hyperacidity to become exaggerated and precipitate a hemorrhage from a peptic ulcer. It is now considered advisable to use antacids in patients on adrenergic blocking agents especially if there is any suggestion of possible ulcer.

For the ordinary ambulatory hypertensive patient in a busy medical practice the only drugs that seem relatively safe and effective are Rauwolfia, veratrum, and hydralazine either alone or in various combinations. Hexamethonium is in an entirely different category because of its widespread actions and side effects as well as its marked hypotensive power especially in patients in the upright position. There have been a number of deaths from the use of this drug but unfortunately these have not been adequately reported in the literature as yet. It seems fair to say that much more investigation should be carried out on such agents by those workers already experienced with them before they are used widely in general practice.

The studies done so far have merely pointed the way to the future when undoubtedly better drugs for treating essential hypertension will be found. Already, however, the physician can take satisfaction in the knowledge that progress is being made, and that today he is not entirely helpless in his approach to the medical therapy of this disease. Indeed he may be of considerable assistance to the surgeon in supplementing with drugs the effects of surgical sympathectomy in patients in whom the results of operation alone have been disappointing. Studies of drug treatment in such cases are also encouraging.

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The opinions and conclusions expressed herein are those of the author and do not necessarily represent the official views of the Scientific Council of the American Heart Association.